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Conflicts of interest and outcomes of clinical trials of antidepressants: An 18-year retrospective study

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ABSTRACT

Pharmaceutical sponsorship, funding sources, and investigators' conflicts of interest may be potential influencers in the conduct and results of clinical trials, as well as in the promotion of psychiatric drug therapies. We report the results of an audit of randomized controlled trials (RCTs) of antidepressants conducted from 2000 to 2017. We searched the Web of Science databases with a comprehensive search strategy to identify phase 2 and 3 RCTs. Out of the 1085 articles initially located, a total of 291 RCTs were identified and included in the final analyses. A higher percentage of RCTs conducted by employees of pharmaceutical companies reported favorable results than those with academic or governmental funding (76.90% vs. 60.60%); however, this association was not significant ($X^2 = 2.47$, $P = 0.18$). The data were further analyzed using bivariate and cluster analytical approaches, and the nonsignificant association persisted in both cases. However, analyses of industry-funded placebo-controlled trials (a subgroup of the 291 RCTs) revealed a higher proportion of results that were reported as significant compared to their counterparts with other funding sources (67% vs. 33%). This association was statistically significant ($X^2 = 9.56$, $P = 0.002$), indicating that there is evidence in support of conflicts of interest as a potential bias in the outcomes of RCTs conducted for antidepressants.

1. Introduction

Pharmaceutical sponsorship, funding sources, and investigators' conflicts of interest are often viewed as potential influencers in the conduct of clinical trials, their results, and the promotion of psychiatric drug therapies (Riaz et al., 2016; Perlis et al., 2005; Martin et al., 2008; Paul and Tauber, 2017; Amiri et al., 2014). There has been particular concern about how relationships between physicians and the pharmaceutical industry may compromise the integrity, independence, scientific rigor, or clinical judgment of physicians and researchers. It is imperative for pharmaceutical industries to employ strategies that ensure huge profit margins, since the stakes and funding involved in new drug development and testing are high. These strategies include rapid recruitment of sufficient number of patients, higher reimbursements to clinical investigators at trial sites, and aggressive marketing of drugs, in addition to providing honoraria, travel grants and direct financial compensation to medical practitioners (Morin et al., 2002; Ahmad et al., 2011).

The role of conflicts of interest in influencing the outcomes of clinical trials has been explored in a number of medical specialties. For example, Riaz et al. (2016) audited 114 trials of cardiovascular drugs, and demonstrated that randomized controlled trials (RCTs) with > 50% of investigators reporting conflicts of interest were more likely to report favorable results. A similar study by Perlis et al. (2005) demonstrated that among 162 RCTs of psychotropic drugs, those that reported conflicts of interest were 4.9 times more likely to report positive results (Perlis et al., 2005). Surprisingly, despite individual cases of pharmaceutical industry misconduct identified in the media, there has been no empirical investigation of clinical trials of antidepressants (Morin et al., 2002; Cosgrove et al., 2017; Moraes et al., 2018). Therefore, this audit was designed to address the paucity of data and investigate how the role of funding agencies and their potential conflicts of interest might influence the outcomes of clinical trials of antidepressants.

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2. Methods

In December 2017, an electronic search was conducted in the Web of Science (WOS) WOS Core Collection, Medline, Korean Journal Database, Russian Science Citation Index and SciELO Citation Index to identify RCTs conducted between 2000 and 2017. The following keywords were used: randomized controlled trial OR RCT OR efficacy OR effectiveness OR trial AND citalopram OR escitalopram OR paroxetine OR fluoxetine OR fluvoxamine OR sertraline OR desvenlafaxine OR duloxetine OR levomilnacipran OR milnacipran OR tofenacin OR venlafaxine OR amitriptyline OR amitriptylinoxide OR clomipramine OR desipramine OR dibenzepin OR dimetacrine OR dosulepin OR doxepin OR imipramine OR lofepramine OR melitracen OR nitroxazepine OR bupropion OR nortriptyline OR noxiptiline OR pipofezine OR protriptyline OR trimipramine OR tricyclic antidepressant* OR selective serotonin reuptake inhibitor* OR serotonin-norepinephrine reuptake inhibitor* OR SSRI OR SNRI OR TCA OR MAOI AND depression OR depressive OR MDD OR major-depress*.

This search identified 1085 RCTs which were scrutinized by three authors for inclusion in the data extraction and analysis. In the first step, 20% of the articles were screened by three reviewers in conjunction with a senior author to assess the level of agreement among the reviewers according to Cohen's kappa (κ), which yielded good inter-rater reliability (κ = 0.82).

In the second step, data were extracted across several matrices including affiliation of the corresponding author, type of funding agency, number of authors with conflicts of interest, nature of the conflicts of interest (honoraria, employment, stockholding, grants), and region where the trail was conducted. The RCTs were categorized into trials with statistically significant results and those with nonsignificant results. The trial results were considered significant if the drug under investigation yielded a statistically significant improvement in the severity of depressive symptoms, and/or was superior to the placebo or usual treatment. Funding organizations and affiliations of corresponding authors were coded as academic/federal or commercial. The year of publication was also noted, to ascertain overall trends in the reporting of conflicts of interest by authors.

All analyses were done with the Statistical Package for Social Sciences (SPSS v.20). Descriptive statistics were calculated for categorical and quantitative variables. The trials were grouped based on the significance of their outcomes and then compared with the chi-squared test of association for different characteristics such as funding organization, affiliation of the corresponding author, and declared conflicts of interest. This was followed by a two-step clustering algorithm which was used to cluster cases based on the results of the trial, number of authors with conflicts of interest, sample size, type of affiliation of the corresponding author, and funding agency.

3. Results

3.1. Characteristics of RCTs

Of the 1085 articles identified in the initial search process, 291 RCTs met the inclusion criteria. The reasons for exclusion were: inappropriate study design (635, 58.5%), not related to antidepressants (18, 1.67%), exploring conditions other than major depression (48, 4.42%), abstracts and posters (52, 4.8%), articles in languages other than English (8, 0.74%), and articles with no full texts available (33, 3.04%). Fig. 1 details the screening process for eligible studies. All citations for eligible studies are provided in Supplementary File 1.

Among the RCTs included, 108 (37.10%) investigated the efficacy of selective serotonin reuptake inhibitors (SSRI), 45 (15.50%) studied selective serotonin and nor-epinephrin reuptake inhibitors (SNRI), 135 (46.39%) tested two or more classes of drugs, and 2 RCTs explored the efficacy of adjuvant alternative medicines or psychotherapies with antidepressants. Only 1 of the trials reported the antidepressant activity of alternative medicine alone. A quarter of RCTs (73, 25.10%) reported the efficacy of antidepressants in major depressive disorders comorbid with other medical conditions. Mean sample size of the trials was 219.50 (223.04), ranging from 18 to 1839 participants. A majority of corresponding authors were affiliated with academic or government institutes (241, 82.8%), while the remainder were affiliated commercial companies (50, 17.2%).

A total of 153 (52.6%) RCTs were funded by academic or government organizations, while 138 (47.4%) were funded by commercial companies. Eli Lilly provided funding for 26 (18.84%) trials, followed by Lundbeck (23, 16.67%), Pfizer (18, 13.04%), GlaxoSmithKline (16, 11.59%), Forest 13 (9.42%), Wyeth (9, 6.52%), Ingelheim (4, 2.90%), Takeda (4, 2.90%), Roche (3, 2.17%), Bristol-Myers Squibb (2, 1.44%) and all others (20, 14.49%). Conflicts of interest were reported by 489 investigators in a total of 115 (39.5%) trials. A total of 56 (40.58%) trials had at least one author employed by the pharmaceutical industry, followed by authors who received grant funding (45, 32.61%) or honoraria (40, 28.99%), who owned stock (28, 20.29%), or who received a salary from a pharmaceutical company (5, 3.62%). Among these 115 articles, conflicts of interest were reported by 1–4 authors in 72 (62.61%) trials, by 5–10 authors in 39 (33.91%) trials, and by more than 10 authors in 4 (3.48%) trials. A majority of trials were conducted in North America (116, 39.90%), followed by Europe (74, 25.53%), Southeast Asia (36, 12.4%), the Middle East (29, 10%), South Asia (10, 3.4%), South America (13, 4.47%), Africa (2, 0.69%), Australia and New Zealand (5, 1.72%), and transcontinental locations (6, 2.06%) (Table 1).

3.2. Overall analyses

First an analysis was conducted for all RCTs irrespective of their number of active treatment arms or the use of alternative medications or psychotherapy as an adjuvant mode of therapy. This showed that a higher proportion of RCTs (175, 60.1%) reported favorable results than unfavorable results. Approximately 67% of commercially-funded projects reported favorable results, versus 59.20% of trials that received academic or governmental funding ($X^2 = 1.03$, $P = 0.32$). Approximately 77% of RCTs conducted by employees of pharmaceutical companies reported favorable results, versus 60.60% of those with authors who received academic or governmental funding ($X^2 = 2.47$, $P = 0.18$). However, these associations were statistically nonsignificant. The chi-squared test of association disclosed a statistically nonsignificant association between the significance of the results and the authors' affiliation ($X^2 = 0.38$, $P = 0.54$), type of funding agency ($X^2 = 0$, $P = 0.99$), and declaring conflicts of interest ($X^2 = 0.04$, $P = 0.84$).

Trials conducted by investigators affiliated with commercial companies had a significantly ($t = -4.35$, $P < 0.001$) higher number of authors (3.36 ± 3.03) who declared conflicts of interest than those funded by academic or governmental agencies (1.33 ± 2.87). A similar trend ($t = -4.91$, $P < 0.001$) was noted for funding agencies: commercially sponsored RCTs reported a higher mean number (2.55 ± 2.78) of authors with conflicts of interest than trials with other sources of funding (0.89 ± 2.97).

There was no significant correlation between year of publication and number of authors reporting conflicts of interest ($r = 0.06$, $P = 0.30$) or sample size (-0.03, $P = 0.58$). However, the point-biserial correlation between more recent year of publication and favorable results was significant ($r = 0.18$, $P = 0.002$). The independent sample *t*-test did not detect an association between the trial results and the number of authors reporting conflicts of interest ($t = -0.32$, $P = 0.75$).

3.3. Placebo-controlled randomized trials

In the next step, a one-sample chi-squared test was used for the 153

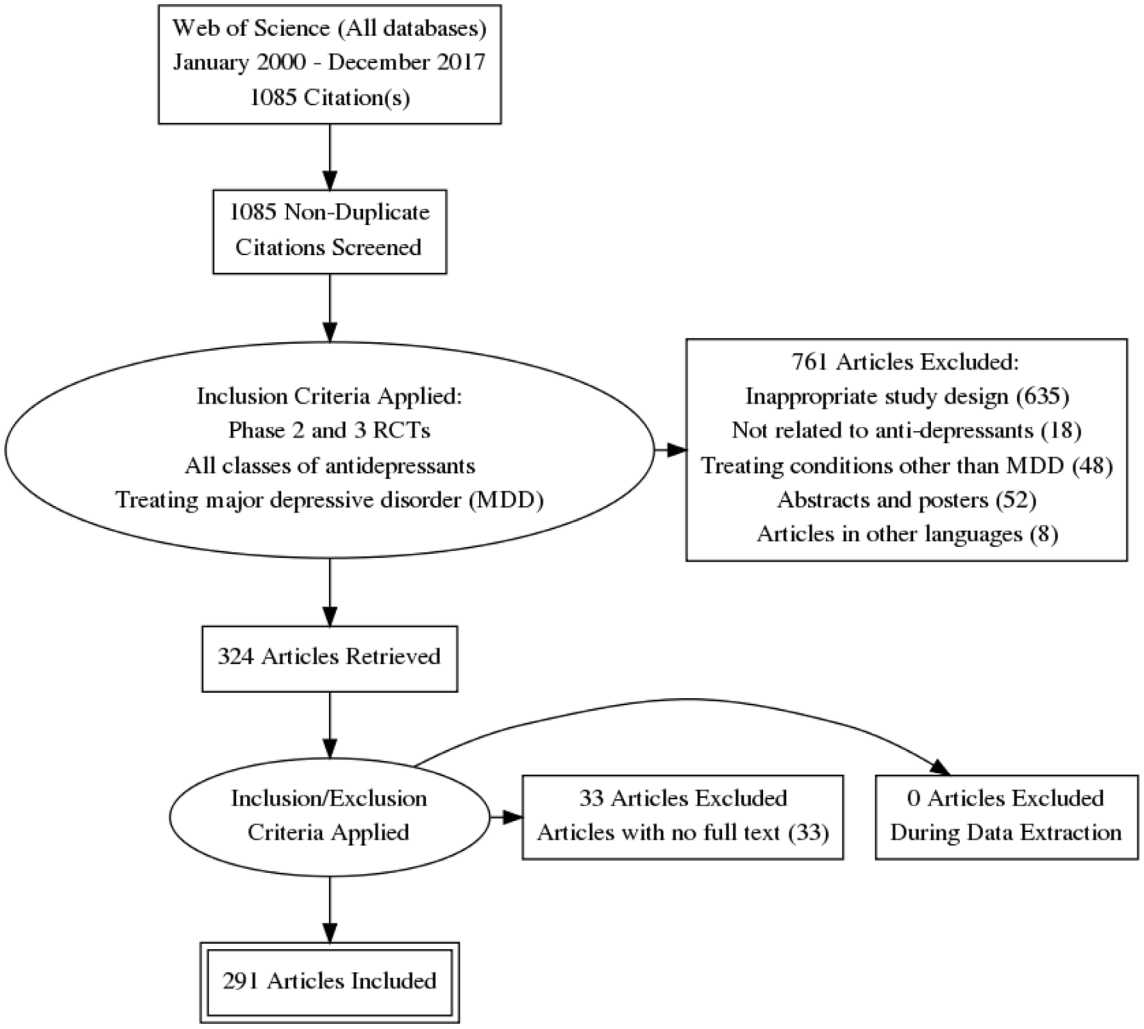

Fig. 1. PRISMA flowchart outlining the study selection and inclusion process, and reasons for inclusion and exclusion.

Table 1
Characteristics of randomized controlled trials included (n = 291).

Variable	Frequency (n)	Percentage (%)
Type of antidepressant		
SSRI	108	37.10
SNRI	45	15.50
≥2 Classes	135	46.39
Region		
North America	116	39.90
Europe	74	25.53
Southeast Asia	36	12.4
Rest of the world	65	22.17
Funding agency		
Commercial	138	47.4
Academic/Government	153	52.6
Trials reporting conflicts of interests	115	39.5
Affiliation of corresponding author		
Commercial	241	82.8
Academic/Government	50	17.2
Sample size (Mean)	219.5 (Range: 18–1839)	–

placebo-controlled RCTs. When the analysis was restricted to these trials, a significantly larger proportion of RCTs reported favorable (97, 63%) than unfavorable (56, 37%) results ($X^2 = 10.99$, $P < 0.001$). Among commercially funded RCTs, a significantly larger proportion (55, 67%) reported favorable than unfavorable (27, 33%) results ($X^2 = 9.56$, $P = 0.002$). However, no statistically significant differences were found between the proportion of favorable (42, 59%) versus unfavorable results (29, 41%) among RCTs that received government or academic funding ($X^2 = 2.38$, $P = 0.123$).

3.4. Two-step clustering analyses

In the final part of the analysis, a two-step clustering algorithm was used to conduct case-based analysis with the following variables: type of funding agency and affiliation, significance of results, number of authors with conflicts of interest, and sample size of the trial. This approach yielded a plausible (good) model with an average silhouette measure of cohesion and separation of 0.7, six independent clusters, and a cluster size ratio of 3.35. The most important predictor of cluster distribution was type of funding agency and institution, followed by significance of the results and authors with conflicts of interest, whereas sample size was the least important predictor. The six clusters did not show a clear-cut pattern in the sets of variables that influenced the statistical significance of RCTs (Table 2, Fig. 2). However, clusters with commercial funding and a higher number of authors reporting conflicts of interest had larger sample sizes and were better designed. Clusters 2 and 3 had the highest numbers of authors with conflicts of interest. Trials in cluster 2, with commercial funding and commercially employed investigators, reported a higher success rate than those in cluster 3, with commercial funding and academic affiliations.

Table 2
Distribution of key variables according to clusters.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Size	59 (20.3%)	37 (12.7%)	42 (14.4%)	53 (18.2%)	23 (7.9%)	77 (26.5%)
Significance of results	100% Significant	64.87% Significant	100% Non-significant	100% Non-significant	65.22% Significant	100% Significant
Funding agency	100% Commercial	100% Commercial	100% Commercial	100% Academic	100% Academic	100% Academic
Institution	100% Academic	100% Commercial	100% Academic	100% academic	56.22% Commercial	100% Academic
Mean number of authors with conflicts of interest	0.06	4.02	1.01	0.03	0.05	0.03
Mean sample size	175.06	341.23	131.81	90.84	257.01	119.07

4. Discussion

This audit did not find a significant association between the role of pharmaceutical sponsorship and the significance of results of RCTs published in the last 18 years. This nonsignificant association persisted in both the bivariate and cluster analyses. However, an analysis of industry-funded placebo-controlled trials showed a higher proportion with favorable results compared to trials with other sources of funding.

The null association between favorable results and conflicts of interest or pharmaceutical sponsorship contrasts with previous findings reported by Perlis et al. (2005). These contradictory findings may be explained by Perlis et al.'s inclusion of a broader category of psychotherapeutic drugs, the limited number of journals they studied (n = 4), and the smaller sample of RCTs in their analysis. However, our finding of a higher proportion of favorable results among industry-funded placebo-controlled trials is in consonance with other previously published evidence.

In contrast to the results of our overall analysis, we found a significant association between source of funding and significance of the results in placebo-controlled trials. This may be due to the fact that a large proportion of trials in the overall analysis compared either two different classes of antidepressants, or two drugs from the same class of antidepressants. Comparisons of two different treatment modalities (for example, intervention group versus treatment as usual or active control group) often lead to diminished effect sizes. Moreover, two different drugs belonging to the same antidepressant class, e.g. those belonging to the SSRI group, may also have similar efficacy, and this can lead to nonsignificant results in the overall analysis. This contrasts with the results from comparisons of an intervention group versus a placebo, a non-active, or a non-treated control group.

Kaplan and Irvin (2015) noted a significant rise in conflicts of interest, industry sponsorship and the provision of medications. To counter the negative implications associated with these factors, recent strides have been made to ensure transparency in the conduct of RCTs, leading to a paradigm shift. Steps taken by stakeholders, such as the public sharing of data, disclosures of conflicting interests, and most importantly a priori registration of RCTs, have made important contributions to transparent trial reporting. Another recent paradigm shift is manifested as the larger number of trials reporting larger sample sizes, and comparing treatment against clinically effective alternatives rather than placebos (Kaplan and Irvin, 2015; Needleman et al., 2008). After the year 2000, game-changing rules were implemented by the International Committee of Medical Journal Editors, such as recommendations to disclose interests and industry co-sponsorship or provision of drugs (Kaplan and Irvin, 2015). Moreover, several quality control measures have been implemented, including recommendations to provide the CONSORT checklist (a diagrammatic presentation of the flow of participants through successive phases of the study) and a priori registration of RCT protocols highlighting the primary outcomes (Milette et al., 2011). The burgeoning need for these recommendations was felt by policy makers and emphasized by various researchers in the field of medicine.

After the establishment of clinicaltrials.gov, it became mandatory for investigators to prospectively register their RCTs, and declare their primary and secondary outcomes. In their study of large trials funded by the National Heart Lung, and Blood Institute (NHLBI), Kaplan and Irvin (2015) assessed a range of variables such as publication year, primary outcomes and the statistical significance of the primary outcome. They demonstrated that the reporting of null results for primary outcomes has increased since the year 2000. Around 57% of studies published prior to 2000 showed a significant benefit of the intervention on the primary outcome, compared to only 8% after 2000. This trend

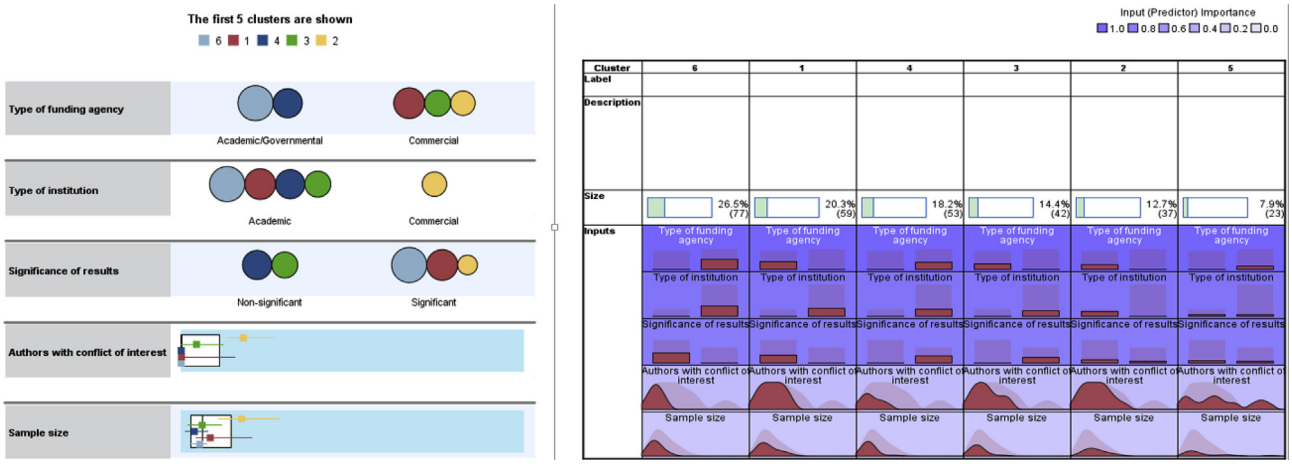

Fig. 2. Detailed groupings of heterogeneous clusters of studies based on the following characteristics: a) significance of results, b) funding agency, c) type of institution, d) mean number of authors with conflicts of interest, and e) mean sample size. Two-step clustering analysis yielded six heterogeneous clusters of studies based on these characteristics. No significant pattern was seen in studies with different sources of funding or the proportion of favorable results.

toward null findings was associated with preregistration at clinicaltrials.gov. The authors argued that this trend may have occurred because prospective registration of RCTs was not required prior to 2000, and this allowed researchers to selectively report statistically significant secondary outcomes rather than statistically null primary outcomes. However, after 2000 there was a rise in prospective registration of RCTs that listed primary outcomes (Kaplan and Irvin, 2015).

Another reason for this paradigm shift may be related to newer clinical trial management techniques implemented to ensure better data collection and more transparent reporting. A relevant example is the recommendation by the Medical Research Council (MRC) in 1998 to establish an independent three-committee structure comprising the Trial Management Group (TMG), the Data Monitoring Committee (DMC) and the executive Trial Steering Committee, in accordance with the MRC Guidelines for Good Clinical Practice (Harman et al., 2015). There has also been a recent drive to report negative and null findings (Oldehinkel, 2018).

This study has some limitations. Firstly, it was limited to RCTs only for antidepressants, so the results cannot be generalized to trials of other psychotherapeutic drugs. Secondly, a total of 33 RCTs could not be audited because the authors could not access their full texts, or because the abstracts reported limited information regarding sponsorship and disclosure of conflicts. Lastly, the sample size was not calculated a priori because this study was designed to include all RCTs that fulfilled the inclusion criteria. Therefore, some statistical tests used to assess the significance of the tested hypotheses may well be underpowered.

In order to improve the quality and credibility of future trials, research-intensive institutes should ensure the implementation of strict protocols to prevent the unethical involvement of commercial funders in the design and execution of RCTs, and in patient recruitment. In order to avoid data manipulation, strict protocols should also be implemented during data analysis. Recruitment, randomization and allocation concealment of patients should be handled by a centralized institutional body independent of the influence of pharmaceutical companies or the study investigators. Prospective trial registration and public sharing of data should be implemented in compliance with both the letter and the spirit of current recommendations for good RCT performance and publication practices.

5. Conclusion

Although a higher percentage of RCTs conducted by employees of pharmaceutical companies reported favorable results than those with academic or governmental funding, this association was found to be nonsignificant. However, the present audit revealed a significant association between industry-funded placebo-controlled trials and statistically significant outcomes of RCTs, indicating that there is evidence in support of conflicts of interest as a potential bias in the outcomes of RCTs conducted to test antidepressants.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Disclosures

There are no disclosures. This study has not been submitted elsewhere for publication.

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Appendix A. Supplementary data

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References

Ahmad, M., Akhtar, N., Awan, M.H., Murtaza, G., 2011. Ethical evaluation of pharmaceutical marketing in Pakistan. Acta Bioeth 17 (2), 215–224.

Amiri, A.R., Kanesalingam, K., Cro, S., Casey, A.T., 2014 Feb 1. Does source of funding and conflict of interest influence the outcome and quality of spinal research? Spine J. 14 (2), 308–314.

Cosgrove, L., Krimsky, S., Wheeler, E.E., Peters, S.M., Brodt, M., Shaughnessy, A.F., 2017 Feb 17. Conflict of interest policies and industry relationships of guideline development group members: a cross-sectional study of clinical practice guidelines for depression. Account. Res. 24 (2), 99–115.

Harman, N.L., Conroy, E.J., Lewis, S.C., Murray, G., Norrie, J., Sydes, M.R., Lane, J.A., Altman, D.G., Baigent, C., Bliss, J.M., Campbell, M.K., 2015 Dec. Exploring the role and function of trial steering committees: results of an expert panel meeting. Trials 16 (1), 597.

Kaplan, R.M., Irvin, V.L., 2015 Aug 5. Likelihood of null effects of large NHLBI clinical trials has increased over time. PLoS One 10 (8), e0132382.

Martin, A., Faraone, S.V., Henderson, S.W., et al., 2008. Conflict of interest. JAACAP 47, 119–120.

Milette, K., Roseman, M., Thombs, B.D., 2011 Mar 1. Transparency of outcome reporting and trial registration of randomized controlled trials in top psychosomatic and behavioral health journals: a systematic review. J. Psychosom. Res. 70 (3), 205–217.

Moraes, F.Y., Mendez, L.C., Taunk, N.K., Raman, S., Suh, J.H., Souhami, L., Slotman, B., Weltman, E., Spratt, D.E., Berlin, A., Marta, G.N., 2018 Feb 1. Funding source, conflict of interest and positive conclusions in neuro-oncology clinical trials. J. Neuro-oncol. 136 (3), 585–593.

Morin, K., Rakatansky, H., Riddick Jr., F.A., Morse, L.J., O'Bannon III, J.M., Goldrich, M.S., Ray, P., Weiss, M., Sade, R.M., Spillman, M.A., 2002 Jan 2. Managing conflicts of interest in the conduct of clinical trials. J. Am. Med. Assoc. 287 (1), 78–84.

Needleman, I., Worthington, H., Moher, D., Schulz, K., Altman, D.G., 2008 Feb 1. Improving the completeness and transparency of reports of randomized trials in oral health: the CONSORT statement. Am. J. Dent. 21 (1), 7.

Oldehinkel, A.J., 2018 Aug. Sweet nothings–the value of negative findings for scientific progress. JCPP (J. Child Psychol. Psychiatry) 59 (8), 829–830.

Paul, C., Tauber, M., 2017 Jan. Conflicts of interest and authorship of industry-sponsored publications. Br. J. Dermatol. 176 (1), 200–203.

Perlis, R.H., Perlis, C.S., Wu, Y., Hwang, C., Joseph, M., Nierenberg, A.A., 2005 Oct 1. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. Am. J. Psychiatry 162 (10), 1957–1960.

Riaz, H., Khan, M.S., Riaz, I.B., Raza, S., Khan, A.R., Krasuski, R.A., 2016 Mar 1. Conflicts of interest and outcomes of cardiovascular trials. Am. J. Cardiol. 117 (5), 858–860.